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802 F.2d 1367
231 U.S.P.Q. 81

HYBRITECH INCORPORATED, Appellant,
v.
MONOCLONAL ANTIBODIES, INC., Appellee.

Appeal No. 86-531.
United States Court of Appeals,
Federal Circuit.
Sept. 19, 1986.

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Douglas E. Olson, Lyon & Lyon, Los Angeles, Cal., for appellant. With him on brief were James W. Geriak and Bradford J. Duft.

David J. Brezner, Flehr, Hohback, Test, Albritton & Herbert, San Francisco, Cal., for appellee. Barry E. Bretschneider and Herbert I. Cantor, Washington, D.C., of counsel.

Before RICH, DAVIS and SMITH, Circuit Judges.

RICH, Circuit Judge.

This appeal is from the August 28, 1985, decision of the United States District Court for the Northern District of California, 623 F.Supp. 1344, 227 USPQ 215, in favor of defendant Monoclonal Antibodies, Inc. (Monoclonal) holding that all 29 claims of plaintiff's patent No. 4,376,110 entitled "Immunometric Assays Using Monoclonal Antibodies" ('110 patent), issued to Dr. Gary S. David and Howard E. Greene and assigned to Hybritech Incorporated (Hybritech), are invalid as anticipated under 35 U.S.C. Sec. 102(g), for obviousness under Sec. 103, and under Sec. 112 first and second paragraphs. We reverse and remand.

Background

Vertebrates defend themselves against invasion by microorganisms by producing antibodies, proteins which can complex with the invading microorganisms and target them for destruction or removal. In fact, any foreign molecule of sufficient size can act as a stimulus for antibody production. Such foreign molecules, or antigens, bear particular sites or epitopes that represent antibody recognition sites. B cell lymphocytes, the cells that actually produce antibodies, recognize and respond to an epitope on an antigen by reproducing or cloning themselves and then producing antibodies specific to that epitope. Even if the antigen is highly purified, the lymphocytes will produce antibodies specific to different epitopes on the antigen and so produce antibodies with different specificities. Furthermore, because the body is exposed to many different antigens, the blood of a vertebrate will contain antibodies to many different antigenic substances.

Scientists and clinicians have long employed the ability of antibodies to recognize and complex with antigens as a tool to

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identify or label particular cells or molecules and to separate them from a mixture. Their source of antibodies has been primarily the serum separated from the blood of a vertebrate immunized or exposed to the antigen. Serum, however, contains a mixture of antibodies directed to numerous antigens and to any number of epitopes on a particular antigen. Because such a mixture of antibodies arises from many different clones of lymphocytes, it is called "polyclonal."

Recent technological advances have made it possible to isolate and cultivate a single clone of lymphocytes to obtain a virtually unlimited supply of antibodies specific to one particular epitope. These antibodies, known as "monoclonal antibodies" because they arise from a single clone of lymphocytes, are produced by a relatively new technology known as the hybridoma. Hybridomas are produced by fusing a particular cancer cell, the myeloma cell, with spleen cells from a mouse that has been injected or immunized with the antigen. These fusions are isolated by transferring them to a growth fluid that kills off the unfused cancer cells, the unfused spleen cells dying off by themselves. The fused hybrid spleen and myeloma cells, called hybridomas, produce antibodies to the antigen initially injected into the mouse. The growth fluid containing the hybridomas is then diluted and put into individual test tubes or wells so that there is only one hybridoma per tube or well. Each hybridoma then reproduces itself and these identical hybridomas each produce identical monoclonal antibodies having the same affinity and specificity. In this way, a virtually unlimited supply of identical antibodies is created, directed to only one epitope on an antigen rather than, as with polyclonal antibodies, to many different epitopes on many different antigens.

In addition to the specificity of antibodies to particular epitopes discussed above, antibodies also have a characteristic "sensitivity," the ability to detect and react to antigens. Sensitivity is expressed in terms of "affinity:" the greater an antibody's ability to bind with a particular antigen, the greater the antibody's affinity. The strength of that antibody-antigen bond is in part dependent upon the antibody's "affinity constant," expressed in liters per mole, for the antigen.

Immunoassays, the subject matter of the '110 patent, are diagnostic methods for determining the presence or amount of antigen in body fluids such as blood or urine by employing the ability of an antibody to recognize and bind to an antigen. Generally, the extent to which the antibody binds to the antigen to be quantitated is an indication of the amount of antigen present in the fluid. Labelling the antibody or, in some cases, the antigen, with either a radioactive substance, I 125, or an enzyme makes possible the detection of the antibody-antigen complex. In an extreme case, where the fluid sample contains a very low level of the antigen, binding might not occur unless the antibodies selected or "screened" for the procedure are highly sensitive.

In the case of a "competitive" immunoassay, a labelled antigen reagent is bound to a limited and known quantity of antibody reagent. After that reaction reaches equilibrium, the antigen to be detected is added to the mixture and competes with the labelled antigen for the limited number of antibody binding sites. The amount of labelled antigen reagent displaced, if any, in this second reaction indicates the quantity of the antigen to be detected present in the fluid sample. All of the antigen attached to the antibody will be labelled antigen if there is no antigen in the test fluid sample. The advantage of this method is that only a small amount of antibody is needed, its drawback, generally, that the system must reach equilibrium, and thus produces results slowly.

In the case of a "sandwich" assay, otherwise known as an immunometric assay, the latter being a term coined by Dr. Lawton Miles in 1971, a quantity of unlabelled antibody reagent is bound to a solid support surface such as the inside wall of a test tube containing a complex of the fluid sample

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containing the antigen to be detected and a labelled antibody reagent. The result is an insoluble three part complex referred to as a sandwich having antibody bread and antigen filling. This figure is illustrative of the sandwich concept:

NOTE: OPINION CONTAINS TABLE OR OTHER DATA THAT IS NOT VIEWABLE

The advantage of the sandwich assay is that it is fast and simple, its drawback that enormous quantities of antibodies are needed.

Hybritech

Hybritech, started in 1978 and joined thereafter by coinventors Green and Dr. David, has, since 1979, been in the business of developing diagnostic kits employing monoclonal antibodies that detect numerous antigens and thus a broad range of conditions such as pregnancy, cancer, growth hormone deficiency, or hepatitis. Examples of antigens include influenza viruses, immunoglobulin E (IgE) which indicates allergic reaction, human chorionic gonadotropin (HCG) which indicates pregnancy, and prostatic acid phosphatase (PAP) which indicates prostate cancer, to name a few. Dr. Adams, a business-experienced scientist, joined the company in May 1980 as head of research and development. The '110 patent, application for which was filed August 4, 1980, issued March 8, 1983, with claims defining a variety of sandwich assays using monoclonal antibodies. Claim 19, apparently the broadest of the twenty-nine in the patent, is directed generally to a sandwich assay and reads (emphasis ours):

19. In an immunometric assay to determine the presence or concentration of an antigenic substance in a sample of a fluid comprising forming a ternary complex of a first labelled antibody, said antigenic substance, and a second antibody said second antibody being bound to a solid carrier insoluble in said fluid wherein the presence of the antigenic substance in the samples is determined by measuring either the amount of labelled antibody bound to the solid carrier or the amount of unreacted labelled antibody, the improvement comprising employing monoclonal antibodies having an affinity for the antigenic substance of at least about 10 8 liters/mole for each of said labelled antibody and said antibody bound to a solid carrier.

Claim 1, directed particularly to a reverse sandwich assay, explained infra, reads:

1. A process for the determination of the presence of [sic, or] concentration of an antigenic substance in a fluid comprising the steps:

(a) contacting a sample of the fluid with a measured amount of a soluble first monoclonal antibody to the antigenic substance in order to form a soluble complex of the antibody and antigenic substance present in said sample, said first monoclonal antibody being labelled;

(b) contacting the soluble complex with a second monoclonal antibody to the antigenic substance, said second monoclonal antibody being bound to a solid carrier, said solid carrier being

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insoluble in said fluid, in order to form an insoluble complex of said first monoclonal antibody, said antigenic substance and said second monoclonal antibody bound to said solid carrier;

(c) separating said solid carrier from the fluid sample and unreacted labelled antibody;

(d) measuring either the amount of labelled antibody associated with the solid carrier or the amount of unreacted labelled antibody; and

(e) relating the amount of labelled antibody measured with the amount of labelled antibody measured for a control sample prepared in accordance with steps (a)-(d), said control sample being known to be free of said antigenic substance, to determine the presence of antigenic substance in said fluid sample, or relating the amount of labelled antibody measured with the amount of labelled antibody measured for samples containing known amounts of antigenic substance prepared in accordance with steps (a)-(d) to determine the concentration of antigenic substance in said fluid sample, the first and second monoclonal antibodies having an affinity for the antigenic substance of at least about 10 8 liters/mole.

The District Court Decision

Hybritech sued Monoclonal March 2, 1984, for damages and an injunction alleging that the manufacture and sale of Monoclonal's diagnostic kits infringed the '110 patent. Trial without a jury began on August 5, 1985, and concluded August 23, 1985, thirty witnesses having been heard and over 2,000 pages of transcript generated. The district court produced the reported opinion, findings, and conclusions, which use nearly verbatim Monoclonal's pre-trial brief and pre-trial proposed findings of fact and conclusions of law, in three days, in support of the judgment now on appeal.

The district court held that the claimed subject matter of the '110 patent was neither conceived nor actually reduced to practice before May 1980, and was anticipated under Sec. 102(g) by the actual reduction to practice of the invention by Drs. Uotila and Ruoslahti at the La Jolla Cancer Research Foundation (LJCRF) as early as November of 1979 and by the actual reduction to practice of the invention by Drs. Oi and Herzenberg (Oi/Herzenberg work) at the Stanford University Laboratory as early as July 1978, later published in December of 1979.

The district court also held the claims of the '110 patent invalid for obviousness from the Oi/Herzenberg work in view of (1) a February 1979 article by M.E. Frankel and W. Gerhard (Frankel article) which discloses high-affinity monoclonal antibodies, and apparently in view of numerous other references including; (2) the work of Nobel Prize winners G. Kohler and C. Milstein disclosing a Nobel Prize-worthy method for producing monoclonal antibodies in vitro (outside the body) published in an August 7, 1975, article; (3) U.S. Patent No. 4,244,940 issued to Jeong et al. disclosing a simultaneous polyclonal assay (Jeong), U.S. Patent No. 4,098,876 to Piasio et al. disclosing a reverse polyclonal sandwich assay (Piasio), U.S. Patent No. 4,016,143 to Schurrs et al. disclosing a forward polyclonal sandwich assay (Schurrs); (4) a July 1979 publication by A.C. Cuello et al. disclosing the use of monoclonal antibodies in competitive assays; and (5) eight articles dated between January 1979 and March 6, 1980, "predicting" that monoclonal antibodies would be used in future immunoassays. 1

The district court also invalidated the patent on various grounds based on 35 U.S.C. Sec. 112, first and second paragraphs, as hereinafter discussed.

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A. The References

1. Kohler and Milstein's Nobel Prize-Winning Work:

Producing Monoclonal Antibodies In Vitro For the

First Time

In early immunoassay work, polyclonal antibodies produced in vivo (in the body) in mice were used to bind with the antigen to be detected in the body fluid sample. Mice were immunized by injection with antigen so that the lymphocytes in their bodies produced antibodies that attacked the injected antigen. Those polyclonal antibodies were withdrawn from the animal's blood and used in immunoassays. The major problem was that when the mice's immune systems changed or the mice died, the antibodies changed or died too; supply was limited and uncertain.

As the examiner was aware, Kohler and Milstein developed a technique not only for producing antibodies in vitro, independent of a living body, thus eliminating dependence on a particular animal, but for in vitro production of monoclonal antibodies by hybridomas, discussed in the Background section, supra.

Given that sandwich assays require enormous amounts of antibodies, companies like appellant and appellee, which utilize monoclonal antibodies for sandwich assays, would not be in business were it not for the work of Kohler and Milstein.

2. The Work of Drs. Ruoslahti, Uotila, and Engvall at the La

Jolla Cancer Research Foundation (LJCRF) in 1979

and 1980

Dr. Ruoslahti performed mostly competitive immunoassays using polyclonal antibodies to alphafetoprotein (AFP) antigens at the City of Hope since 1970. Dr. Uotila joined him in late 1978 to perform immunoassays using monoclonal antibodies to AFP. After producing monoclonal antibodies to AFP and performing competitive radio immunoassays (RIA--a competitive assay that uses a radioactive label) with monoclonal antibodies at the City of Hope in mid-1979, Drs. Ruoslahti, Uotila and Engvall left LJCRF.

In the fall of 1979, September or October according to Dr. Uotila, discussion and work began on using monoclonal antibodies to AFP in a sandwich assay. Dr. Uotila, the principal researcher in this particular endeavor, generated six notebooks while at the City of Hope and LJCRF. The next-to-last page of notebook four contained a note to Dr. Uotila from Dr. Ruoslahti reading:

Sometime you should enzyme label a good monoclonal antibody so that you can set up a sandwich assay. If you use two monoclonal antibodies, you may be able to do the assay with a single incubation, since the monoclonal antibodies are likely to be directed against different determinants and not compete with one another.

Although Dr. Uotila's notebook pages were, for the most part, unsigned, undated, and uncorroborated, Dr. Ruoslahti's testimony, placed the date of this note at about October 1979 by referring to the first pages of notebook five which were dated in early November 1979. Dr. Ruoslahti testified that one curve on one graph on page 43D of notebook five showed a successful simultaneous sandwich assay using monoclonal antibodies about November 5, 1979, although no data supporting that graph could be found elsewhere in the notebook. He further testified that the affinity of the monoclonal antibodies used for that test was not calculated until 1980 but that the raw data necessary for that calculation was generated in 1979.

Dr. Uotila stated in her deposition (she did not testify at trial) that she started work on a sandwich assay using monoclonal antibodies between October 4 and the end of that month, 1979, and that she could not remember the procedure used nor was there enough information in her notebook, including page 43D, to refresh her memory. She did remember, although she continued work on this assay because the tests did not yield repeatedly good curves without which she would not publish her work, that the assay on page 43D was successful. Dr. Engvall testified about a discussion of Dr. Uotila's monoclonal antibody work with

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her while at the City of Hope and about first performing a sandwich assay after arriving at LJCRF in 1979.

3. The Work of Drs. Oi and Herzenberg at the Stanford

University Laboratory in 1978 Published in

December 1979

Drs. Oi and Herzenberg used monoclonal antibodies to "map" epitopes or determine the number and location of different antibody binding sites on a known quantity of IgE antigen by attaching to it an antibody bound to a carrier and exposing that antigen to other monoclonal antibodies. The antibodies either attached to epitopes on the antigen or were blocked from doing so by the other monoclonal antibodies, depending on the location and number of epitopes; if the epitopes on the antigen were too close together and the number of antibodies too great, few antibodies would bind to the antigen. Hybritech points out that both Dr. Herzenberg

and Dr. Oi testified that their work did not involve determining the presence or quantity of antigen, that they had no idea what the affinities of the monoclonal antibodies used were, and that those values were never calculated.

One unsigned, unwitnessed page from three large laboratory notebooks, which Hybritech argues is insufficient because it does not identify the chemical reagents or protocol used, was relied on by Monoclonal to establish actual reduction to practice of the Oi/Herzenberg work in 1978 to establish a case of Sec. 102(g) prior invention by another. The district court agreed with Monoclonal that the Oi/Herzenberg work anticipated the claimed invention and, in addition, combined this work with the Frankel publication to hold that the claimed subject matter was obvious under Sec. 103.

4. The Frankel Article: Monoclonal Antibodies Having

Affinities of 10 9 liters/mole

Frankel describes an RIA (radioimmunoassay) method for the rapid determination of affinity constants for monoclonal antibodies produced from hybridomas. The article states that the assay used is applicable only to antibodies with binding constants of about 10 10 liters/mole and discloses the binding constants for antibodies to several closely related strains of influenza virus.

The district court found that Frankel disclosed monoclonal antibodies having the affinity constants claimed in the '110 patent, 10 8 to over 10 9 liters/mole.

5. The Cuello Article and the Jeong, Piasio, and Schurr

Patents Considered by the Examiner

Cuello, dated July 1979, states that it describes the usefulness of monoclonal antibodies in the characterization and localization of neurotransmitters such as Substance P, a peptide clearly associated with the transmission of primary sensory information in the spinal cord. The article discloses producing monoclonal antibodies from hybrid myelomas (hybridomas), their use in conventional radioimmunoassay techniques, and the benefits from doing so which flow from the ability to derive permanent cell lines capable of continuous production of highly specific antibodies.

The district court found that the examiner twice rejected all of the claims of the '110 patent based on Cuello alone or in combination with the Jeong, Piasio, and Schurr references which disclose various sandwich assays using polyclonal antibodies. The court also found that the examiner allowed the claims after they were amended to include the 10 8 affinity limitation and after Richard Bartholomew, a Hybritech employee, submitted an affidavit alleging the advantages of using monoclonal rather than polyclonal antibodies in sandwich assays.

Apparently based on the testimony of Monoclonal's expert witness Judith Blakemore, a named inventor of the Jeong patent, manager of antibody programs at Bio-Rad Laboratories from 1975 to 1982, and currently manager of monoclonal antibody therapeutics at Cetus Corporation, a Hybritech competitor in immunoassay diagnostics, the district court stated that the "reasons for allowance were not well-founded because (1) the alleged advantages were

expected as naturally flowing from the well-known natural characteristics of monoclonal antibodies ...; (2) ... were not significant ...; or (3) were at best minor," although they were "argued to the examiner as if they were" important. These were Monoclonal's words from its pretrial submission adopted by the court.

6. The References That "Predicted" the Use of Monoclonal

Antibodies in Immunoassays

The district court stated, again in Monoclonal's words, that "it is of the utmost importance" that the advantages of monoclonal antibodies were "predicted by a number of authorities," eight to be exact, not important enough to list here, after the Kohler and Milstein discovery and after monoclonal antibodies became available.

B. The Claimed Subject Matter of the '110 Patent

Hybritech argues that the district court's determination that there is no credible evidence of conception or reduction to practice of the '110 invention before May 1980 is error because Dr. David's laboratory notebooks, Nos. 21 and 24, clearly show successful sandwich assays using monoclonal antibodies in August, September, and October of 1979. At the least, argues Hybritech, the invention was conceived in January of 1979, long before Drs. Ruoslahti, Engvall, and Uotila began work on a sandwich assay using monoclonal antibodies, and diligence was thereafter exercised until constructive reduction to practice occurred by the filing of the '110 patent application on August 4, 1980.

Dr. David and Greene testified that pages 2118 to 2122 of Dr. David's notebook, dated January 4, 1979, and witnessed January 30, 1979, disclose the generic conception of the invention in the context of the physical support structure used to carry out a sandwich assay, and Dr. David testified on redirect that (1) Page 1128 of notebook 21, dated May 27, 1979, recorded an early attempt at a sandwich assay that failed, (2) on August 3, 1979, as recorded at page 1166, a sandwich assay using monoclonal antibody 068 attached to a solid carrier, a radio-labelled 068 antibody, and a hepatitis antigen from an Abbott Labs polyclonal competitive assay kit was successfully performed, and (3) a sandwich assay using a bound 259 antibody, a radio-labelled 068 antibody, and a hepatitis antigen was successfully performed on September 21, 1979. Hybritech also urges that work in October 1979 directed to determining whether certain monoclonal antibodies were recognizing the same or different determinants, was a reduction to practice.

Monoclonal points out that these notebook pages do not expressly state that monoclonal antibodies of 10 8 liters/mole affinity were used in a sandwich assay and that the May, August, and September notebook entries were not witnessed until about the time Dr. Adams, experienced in patent matters, joined Hybritech and advised its researchers on properly recording laboratory work. They therefore claim that actual reduction to practice was not shown before May 1980.

OPINION

I. Review Under Rule 52(a) Fed.R.Civ.P.

Rule 52(a) "ensures care in the preparation of an opinion ... and provides appellate courts with the benefit of the District Court's insights into a case," Pentec, Inc. v. Graphic Controls Corp., 776 F.2d 309, 318, 227 USPQ 766, 772 (Fed.Cir.1985) (Harvey, Senior District Judge, concurring) by requiring a district court to "find the facts specially and state separately its conclusions of law thereon." With the exception of the first eight paragraphs, the first half of the district court's opinion here is Monoclonal's pretrial brief and the last three pages of the opinion are Monoclonal's pretrial findings of fact and conclusions of law. The district court adopted the above documents virtually verbatim, with the exception of portions of each concerning inequitable conduct and noninfringement, apparently without inviting a response from Hybritech, resulting in a repetitious (as the district court admitted in

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the opinion), sometimes internally inconsistent, and hard to follow opinion that presents us with a difficult task in gleaning the basis for many of the conclusions. For some of the findings, submitted before trial, no supporting evidence was introduced at trial.

The Supreme Court, in Anderson v. City of Bessemer City, N.C., 470 U.S. 564, 105 S.Ct. 1504, 84 L.Ed.2d 518 (1985), strongly criticized the practice of "verbatim adoption of findings of fact prepared by prevailing parties, particularly when those findings have taken the form of conclusory statements unsupported by citation to the record." Anderson, supra, 105 S.Ct. at 1511. This court also has cautioned against the adoption of findings, especially when proposed by a party before trial, as here, and stated that the likelihood of clear error in those findings increases in such a situation. Lindemann Maschinenfabrik v. American Hoist and Derrick, 730 F.2d 1452, 1457, 221 USPQ 481, 485 (Fed.Cir.1984). Notwithstanding our misgivings about whether the findings in this case, prepared before any evidence was introduced, satisfy the objectives of Rule 52(a)--a carefully prepared opinion providing the reviewing court with the benefit of the district court's reasoned insights into the case--those findings are the district court's and may be reversed only if clearly erroneous. See Anderson, supra, 105 S.Ct. at 1511; Lindemann, 730 F.2d at 1457, 221 USPQ at 485.

"A finding is clearly erroneous when, although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." United States v. United States Gypsum Co., 333 U.S. 364, 395, 68 S.Ct. 525, 542, 92 L.Ed. 746 (1948). "This standard plainly does not entitle a reviewing court to reverse the finding of the trier of fact simply because it is convinced that it would have decided the case differently." Anderson, supra, 105 S.Ct. at 1511. In other words, "if the district court's account of the evidence is plausible in light of the record viewed in its entirety" or "where there are two permissible views of the evidence," the factfinder cannot be clearly erroneous. Anderson, supra, at 1511 (quoting United States v. Yellow Cab Co., 338 U.S. 338, 342, 70 S.Ct. 177, 179, 94 L.Ed. 150 (1949)). This is so, stated the Court in dictum, see Anderson, supra, 105 S.Ct. at 1516 (Blackmun, J., concurring), even when the district court's findings rest on physical or documentary evidence or inferences from other facts and not on credibility determinations. See also Rule 52(a) Fed.R.Civ.P. (as amended Aug. 1, 1985). If the latter are involved, "Rule 52 demands even greater deference to the trial court's findings" but a trial judge may not "insulate his findings from review by denominating them credibility determinations"; if documents or objective evidence contradict the witness's story, clear error may be found even in a finding purportedly based on a credibility determination. Anderson, supra, at 1512-13. We proceed in light of all these principles.

II. Presumption of Validity

Under 35 U.S.C. Sec. 282, a patent is presumed valid, and the one attacking validity has the burden of proving invalidity by clear and convincing evidence. See, e.g., American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1360, 220 USPQ 763, 770 (Fed.Cir.1984). Notwithstanding that the introduction of prior art not before the examiner may facilitate the challenger's meeting the burden of proof on invalidity, the presumption remains intact and on the challenger throughout the litigation, and the clear and convincing standard does not change. See, e.g., Jervis B. Webb Co. v. Southern Systems, Inc., 742 F.2d 1388, 1392 & n. 4, 222 USPQ 943, 945 & n. 4 (Fed.Cir.1984). The only indication that the district court recognized the presumption of validity and its proper application was its statement that "[t]he key issue in this case is whether the defendant has overcome the presumption of nonobviousness." That statement, however, speaks only part of the truth; the presumption of validity goes to validity of the patent in relation to the patent statute as a whole, not just to nonobviousness under section 103.

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III. Prior Invention of Another, 35 U.S.C. Sec. 102(g)

Section 102(g) states that a person shall be entitled to a patent unless "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it." Section 102(g) "relates to prior inventorship by another in this country" and "retains the rules governing the determination of priority of invention...." Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1444, 223 USPQ 603, 606 (Fed.Cir.1984) (quoting P.J. Federico, Commentary on the New Patent Act, 35 USCA page 1, at 19 (1954)). Section 102(g) says: "In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other."

Reduction to practice, and conception as well, is a legal determination subject to review free of the clearly erroneous standard. Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd., 731 F.2d 831, 837, 221 USPQ 561, 565-66 (Fed.Cir.1984); D.L. Auld Co. v. Chroma Graphics Corp., 714 F.2d 1144, 1151, 219 USPQ 13, 18 (Fed.Cir.1983). Findings of fact supporting that legal conclusion are, of course, reviewed under the clearly erroneous standard.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." 1 Robinson On Patents 532 (1890); Coleman v. Dines, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed.Cir.1985). Actual reduction to practice requires that the claimed invention work for its intended purpose, see, e.g., Great Northern Corp. v. Davis Core & Pad Co., 782 F.2d 159, 165, 228 USPQ 356, 358, (Fed.Cir.1986), and, as has long been the law, constructive reduction to practice occurs when a patent application on the claimed invention is filed. Weil v. Fritz, 572 F.2d 856, 865 n. 16, 196 USPQ 600, 608 n. 16 (CCPA 1978) (citing with approval Automatic Weighing Machine Co. v. Pneumatic Scale Corp., 166 F. 288 (1st Cir.1909)).

After a review of the record in its entirety, including the numerous corroborating Hybritech laboratory notebooks, internal documents, and pertinent testimony, we hold clearly erroneous the district court's finding that there is no clear or corroborated evidence "with regard to when before May 1980, the idea of actually using monoclonals in sandwich assays" was conceived or, more properly, or when the claimed invention was conceived, and therefore reverse the court's holding, as a matter of law, that Hybritech's inventors did not conceive the claimed invention before May 1980.

Hybritech's claim of conception, generally, is evidenced by the sometimes sparsely documented work of a start-up company whose first small advances evolved into the myriad activities of a mature company with efforts directed toward developing the claimed invention by first employing the Kohler and Milstein technology to produce the necessary monoclonal antibodies and using those antibodies in diagnostic sandwich assay kits. There is no doubt that exploiting monoclonal antibodies for use in sandwich assays was one of the major objectives of Hybritech. In a letter to Pharmacia Fine Chemicals dated April 26, 1979, Greene, in responding to Pharmacia's interest in Hybritech's products, outlined the latter's "efforts to bring the exciting new hybridoma technology into routine medical use" and its exploration of "several intriguing concepts for which monoclonals may open up new immunodiagnostic techniques heretofore infeasible with animal serums." Although company minutes in early 1979 contain little about the claimed subject matter and some of the discussions thereon, such as Greene's and Dr. Adams' conversation about monoclonal sandwich assays when the former was trying to woo Dr. Adams to join Hybritech were unrecorded, the Hybritech laboratory notebooks and the

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nature of Hybritech's research program fully corroborate the testimonial evidence of conception and thus clearly support our holding that Hybritech conceived the claimed invention before LJCRF.

Dr. David's January 1979 notebook describes, in detail, as explained by Greene and Dr. David at trial, a nylon apparatus that undoubtedly could be used for performing a sandwich assay using monoclonal antibodies, although Dr. David testified on cross-examination that at that time Hybritech had not yet developed any monoclonal antibodies, including attaching one of the reagents to a solid carrier ring, contacting that ring with a fluid sample in a microtiter plate well, adding a labelled reagent to the well after rinsing, and then "counting" or measuring the amount of either the labelled or unlabelled reagent after a prescribed time and second rinsing. The notebook then describes the procedure for detecting an antibody "(a-x)" to an antigen "(x)" complete with diagrams and text, both illuminated by Dr. David at trial. The notebook further states, "Alternatively, if one wished to quantitate an antigen, y, the identical procedure would be followed, except that reagents would be reversed, i.e. the reaction would be:" and there follows a clear illustration of an antibody attached to a solid carrier reacting with an antigen to form a complex, and that complex reacting with a second labelled antibody. The notebook was signed by Dr. David on January 4, 1979, and witnessed and signed on January 30 of the same year by Dr. Curry, the first cell biologist hired at Hybritech to set up the hybridoma production program.

Dr. David testified on direct that monoclonal antibodies were developed in the following months: antigens were purchased from outside sources and purified before being injected into mice; the spleen cells from those mice were fused with myelomas; and the resultant hybridomas were separated into well plates for development, and a radioimmunoassay procedure was carried out to determine the affinity of the antibodies.

The May 1979 failed sandwich assay, witnessed in May 1980, corroborates Dr. David's testimony that a polyclonal antibody bound to a solid carrier and a labelled monoclonal antibody were used in a sandwich assay with an antigen from Abbott Labs' Ausria polyclonal diagnostic kit for hepatitis. No binding was detected.

Dr. David testified about the experiment documented in the August 1979 notebook, a sandwich assay with a hepatitis antigen from an Abbott Labs Ausria kit with two Hybritech 068 monoclonal antibodies, one attached to a solid carrier bead and the other labelled; the purpose of the experiment was to quantitate the antigen. The notebook corroborates Dr. David's testimony that the test was positive and lists the counts per minute of the labelled antibody. Defendant Monoclonal's expert Ciotti testified about this experiment:

Also, of course, it is limited to--it is limited to hepatitis antigen. And without a generic conception, it would just be merely a--if it did work for its intended purpose--which I would assume for purposes of discussion--it would be a reduction to practice of one embodiment. And without a corresponding generic conception, I don't think it would be held to be the making of the invention in terms of, for instance, in claim 19. [Emphasis ours.]

Dr. David further testified that the September 21, 1979, record in David's notebook, witnessed months later, shows a reverse sandwich assay using a bound 259 monoclonal antibody and a labelled 068 monoclonal antibody with a hepatitis antigen with results confirmed by a dose response curve. 2 Hybritech further alleges that a laboratory notebook page dated October 1979 is a reduction to practice of the

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claimed invention but fails to cite any related testimony or other evidence in support thereof.

Finally, the record shows that the claimed affinity limitation "of at least about 10 8 liters/mole" was determined and appreciated during the course of the development of the claimed subject matter. Dr. David and Dr. Adams separately testified that the screening procedures used by Hybritech ensured that only monoclonal antibodies having at least 10 8 liters/mole affinity would be used in assays. An October 1979 internal memorandum from Greene to the staff states, "To improve comparisons we will express all affinities to the base ten to the eighth which represents the lower end of the useable range."

We are left with the definite and firm conviction that a mistake has been committed because the district court's account of the evidence that "there was no credible evidence of conception before May 1980" is insupportable. There is such evidence. The laboratory notebooks, alone, are enough to show clear error in the findings that underlie the holding that the invention was not conceived before May 1980. That some of the notebooks were not witnessed until a few months to one year after their writing does not make them incredible or necessarily of little corroborative value. Admittedly, Hybritech was a young, growing company in 1979 that failed to have witnesses sign the inventors' notebooks contemporaneously with their writing. Under a reasoned analysis and evaluation of all pertinent evidence, however, we cannot ignore that Hybritech, within a reasonable time thereafter, prudently had researchers other than those who performed the particular experiments witness the notebooks in response to Tom Adams' advice. The notebooks clearly show facts underlying and contemporaneous with conception of the claimed invention and in conjunction with the testimony of Dr. David and Greene, and others, are altogether legally adequate documentary evidence, under the law pertaining to conception, of the formation in the minds of the inventors of a definite and permanent idea of the complete and operative invention as it was thereafter applied in practice. We thus are not moved by Monoclonal's argument that the findings of fact underlying conception are based on credibility determinations and are more sacrosanct than usual. See Anderson, supra, 105 S.Ct. at 1512-13.

1. LJCRF Is Not Prior Art

Hybritech laboratory notebooks and the uncontradicted testimony of Dr. David and Mr. Greene show that development of the claimed invention proceeded diligently through the rest of 1979 and 1980, there being absolutely no evidence of record nor even argument by Monoclonal that Hybritech was not diligent in its efforts to reduce to practice the claimed invention during the period January 1979 to the '110 application filing date of August 4, 1980. We therefore hold as a matter of law that Hybritech's conception, which was before LJCRF conceived the claimed invention, coupled by diligence to its constructive reduction to practice by the filing of the '110 application, entitle Hybritech to priority over LJCRF. See 35 U.S.C. Sec. 102(g). The work of LJCRF is therefore not prior art.

We also note that there is inadequate factual basis for the district court's holding that LJCRF reduced the claimed invention to practice as early as November 1979 because the only evidence that corroborates the testimony of Ruoslahti, Uotila, and Engvall is the note from Ruoslahti to Uotila, see section A, 2, supra, which indisputably is not the claimed invention, and the one curve from one graph from only one page, 43D, of the six Uotila notebooks. After a reasoned examination, analysis, and evaluation of this pertinent evidence we conclude that it falls far short of showing the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice," see Coleman, 754 F.2d at 359, 224 USPQ at 862, and therefore is legally inadequate to support even a holding of conception of

the claimed invention by LJCRF personnel in 1979.

(1) It is undisputed that page 43D was not signed, witnessed, or dated; (2) the deposition testimony of Uotila was that she could not remember the procedure used to arrive at the dose-response curve on page 43D and there was not enough information in her notebook to refresh her memory; (3) the testimony of Ruoslahti was that he could find no data in the notebook supporting that graph, none of the later graphs shown there represented successful assays and that "especially after this was done, we ran into more severe problems. And it took us a while to do away with the problems;" (4) Ruoslahti also testified that they never determined, in 1979, the affinities of the monoclonal antibodies they used, and that the title of page 43D had been altered at some point--the word "inhibition" had been crossed out and "sandwich" written in; and (5) the testimony of Engvall was that there was nothing about the shape of those curves which indicates that they were sandwich assays. We also note, as evidence bearing upon the credibility of Ruoslahti's testimony (that LJCRF actually reduced the claimed invention to practice in 1979), that when LJCRF attempted to provoke an interference in the PTO with Hybritech based on the U.S. filing of an application that was the counterpart to a Swedish application disclosing similar subject matter, LJCRF could not demonstrate even a prima facie reduction to practice prior to Hybritech's August 4, 1980, filing date. During that proceeding, the earliest dates Ruoslahti set down on paper to support conception and reduction to practice were in 1980.

2. The Work of Oi/Herzenberg Is Not the Claimed Invention

It is axiomatic that for prior art to anticipate under Sec. 102 it has to meet every element of the claimed invention, and that such a determination is one of fact. See, e.g., Lindemann, supra, 730 F.2d at 1458, 221 USPQ at 485; Great Northern Corp. v. Davis Core & Pad Co., 782 F.2d 159, 165, 228 USPQ 356, 358 (Fed.Cir.1986). Section 102(g) upon which the district court relied is one type of "anticipation," i.e., prior invention by another of the same invention. Drs. Oi and Herzenberg testified that their work did not involve detecting the presence of or quantitating antigen but a determination of the number and location of epitopes on a known quantity of antigen. Although this work did involve a sandwich assay to the extent that an antigen was sandwiched between two monoclonal antibodies, it is clear that the similarity between that work and the claimed invention goes no further. Furthermore, both doctors testified that they did not know the affinities of the antibodies that were used in their mapping work and in fact never calculated them. Ciotti, Monoclonal's expert, testified that the 10 8 affinity limitation cannot be found anywhere in the Oi/Herzenberg work. Again we are left with a definite and firm conviction that a mistake was made because that work does not meet every element of the claimed invention. The district court's finding to the contrary is clearly erroneous.

We note that the district court, in also holding the patent invalid under Sec. 103, next considered, combined the Oi/Herzenberg work with the Frankel reference, one justifiable inference therefrom being that the court recognized that Frankel discloses a claim element that Oi/Herzenberg does not, namely, at least about 10 8 liters/mole affinity.

IV. Obviousness, 35 U.S.C. Sec. 103

A section 103 obviousness determination--whether the claimed invention would have been (not "would be" as the court repeatedly stated because Monoclonal's pretrial papers used that improper language) obvious at the time the invention was made is reviewed free of the clearly erroneous standard although the underlying factual inquiries--scope and content of the prior art, level of ordinary skill in the art, 3 and differences between the prior art

fastcase

and the claimed invention--integral parts of the subjective determination involved in Sec. 103, are reviewed under that standard. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached and is not merely "icing on the cake," as the district court stated at trial. See Lindemann, supra, 730 F.2d at 1461, 221 USPQ at 488; Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed.Cir.1983); Kansas Jack, Inc. v. Kuhn, 719 F.2d 1144, 219 USPQ 856 (Fed.Cir.1983); W.L. Gore & Associates v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303, 314 (Fed.Cir.1983).

1. The Eight Articles "Predicting" Widespread Use of

Monoclonal Antibodies

Before discussing the more pertinent references in this case--the Oi/Herzenberg and Frankel works--we cull the other prior art references relied on by the trial court.

First, the latest four of the eight articles that the court stated were of the "utmost importance" because they "predicted" that the breakthrough in production of monoclonal antibodies by Kohler and Milstein would lead to widespread use of monoclonal antibodies in immunoassays are neither 102(a)/103 nor 102(b)/103 prior art because they are dated between late 1979 and March 6, 1980, well after the date of conception and within one year of the filing date of the '110 patent.

The earliest four of the eight articles, on the other hand, although clearly prior art, discuss production of monoclonal antibodies--admittedly old after Kohler and Milstein showed how to produce them--but none discloses sandwich assays. At most, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished. To the extent the district court relied upon these references to establish that it would have been obvious to try monoclonal antibodies of 10 8 liters/mole affinity in a sandwich immunoassay that detects the presence of or quantitates antigen, the court was in error. See Jones v. Hardy, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed.Cir.1984) ("Obvious to try" is improper consideration in adjudicating obviousness issue). 4

2. The Kohler and Milstein Work, the Cuello Article and the

Jeong, Piasio, and Schurr Patents Considered by

the Examiner

The district court's finding that Kohler and Milstein developed a method for producing monoclonal antibodies in vitro is correct, but that finding proves no more; although it made possible all later work in that it paved the way for a supply of monoclonal antibodies, it indisputably does not suggest using monoclonal antibodies in a sandwich assay in accordance with the invention claimed in the '110 patent.

The Cuello reference discloses monoclonal antibodies but not in a sandwich assay. The competitive assay in Cuello, moreover,

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uses only one monoclonal antibody and thus in no way suggests the claimed invention wherein a ternary complex of two monoclonal antibodies and an antigen form a sandwich. Furthermore, the court did not explain how this art, by itself or in combination with any of the other art, suggests the claimed subject matter and thus why that combination would have been obvious. We are of the opinion that it does not.

The district court correctly found that the use of polyclonal antibodies in sandwich assays was well known. The Jeong patent discloses the use of polyclonal antibodies in a simultaneous sandwich assay, with no suggestion that monoclonal antibodies be so used. It is prior art by virtue of Sec. 102(e), application for the patent having been filed September 5, 1978, its effective date as a reference. The Piasio patent, disclosing a reverse sandwich assay using

polyclonal antibodies, and Schurrs, disclosing a forward sandwich assay using the same, both Sec. 102(a) prior art, are likewise devoid of any suggestion that monoclonal antibodies can be used in a similar fashion.

3. The Oi/Herzenberg Work and the Frankel Article

Clearly, the most pertinent items of prior art not cited by the examiner are the Oi/Herzenberg work, as described in section A, 3, supra, and the Frankel article. As stated in the discussion of Prior Invention of Another (section III, 2, supra), the Oi/Herzenberg work involved mapping epitopes on a known quantity of antigen. It was not concerned with and does not disclose using monoclonal antibodies of at least 10 8 liters/mole affinity. Oi and Herzenberg testified that they did not know the affinity of the antibodies used, and Ciotti testified that nowhere in that work is there mention of monoclonal antibody affinity of at least 10 8 liters/mole. On this basis, we conclude that the Oi/Herzenberg work is qualitatively different than the claimed invention; the former is directed to mapping epitopes on a known quantity of antigen and the latter to determining the "presence or concentration of an antigenic substance in a sample of fluid...." We disagree with Monoclonal that these are "essentially the same thing." Furthermore, it is perfectly clear that this work in no way suggests using monoclonal antibodies of the affinity claimed in the '110 patent. It is because of these differences between the Oi/Herzenberg work and the claimed invention that the fact that an antigen was sandwiched between two monoclonal antibodies in the course of Oi's and Herzenberg's work is not sufficient basis to conclude that the claimed invention would have been obvious at the time it was made to a person of ordinary skill in the art.

Likewise, a conclusion that the invention would have been obvious cannot properly be reached when the Oi/Herzenberg work is considered in view of the Frankel article. Frankel teaches a method for rapid determination of affinity constants for monoclonal antibodies, some of which clearly have affinities of the order defined by the claims, but does not in any way suggest using two of those antibodies in a sandwich to assay an antigen by forming a ternary complex of labelled antibody, the antigenic substance, and a bound antibody wherein the presence of the antigenic substance is determined by measuring either the amount of labelled antibody bound to a solid carrier or the amount of unreacted labelled antibody. The mere existence of prior art disclosing how to measure the affinity of high affinity monoclonal antibodies is insufficient to support a holding of obviousness. Hybritech's claims define a process that employs monoclonal antibodies, and does not merely claim antibodies of high affinity. In view of the fact that the Oi/Herzenberg work is not directed to an assay as claimed and does not disclose antibodies of at least 10 8 liters/mole affinity, and further that Frankel fails to suggest using such antibodies in a sandwich assay, the Frankel article does not compensate for the substantial difference between the Oi/Herzenberg work and the claimed subject matter, and therefore those references in combination cannot support a holding of obviousness.

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4. Objective Evidence of Nonobviousness

In one part of its opinion the court found that "the commercial success of the kits may well be attributed to the business expertise and acumen of the plaintiff's personnel, together with its capital base and marketing abilities" (emphasis ours) and later that "[w]here commercial success is based on the sudden availability of starting materials, in this instance the availability of monoclonal antibodies as a result of the Kohler and Milstein discovery, business acumen, marketing ability, and capital sources, no causal relationship is proven." (Citation omitted.)

i. Commercial Success: Hybritech's Diagnostic Kits Grabbed

a Substantial Market Share

The undisputed evidence is that Hybritech's diagnostic kits had a substantial market impact. The first diagnostic kit sales occurring in mid-1981, sales increased seven million dollars in just over one year, from $6.9 million in 1983 to an estimated $14.5 million in 1984; sales in 1980 were nonexistent. Competing with products from industry giants such as Abbott Labs, Hoffman LaRoche, Becton-Dickinson, and Baxter-Travenol, Hybritech's HCG kit became the market leader with roughly twenty-five percent of the market at the expense of market shares of the other companies. Its PAP kit ranks second only to a product sold by Dupont's New England Nuclear, surpassing products from Baxter-Travenol, Abbott, and others. Hybritech's other kits, indisputably embodying the invention claimed in the '110 patent, obtained similar substantial market positions.

Although the district court did not provide its insights into why commercial success was due to business acumen and not to the merits of the claimed invention, Monoclonal urges in support that it was due to Hybritech's spending disproportionate sums on marketing, 25-30% of income. The undisputed evidence was that expenditures of mature companies in this field are between 17 and 32%. Furthermore, the record shows that advertising makes those in the industry--hospitals, doctors, and clinical laboratories--aware of the diagnostic kits but does not make these potential users buy them; the products have to work, and there is no evidence that that is not the case here or that the success was not due to the merits of the claimed sandwich assays--clearly contrary to the district court's finding.

The trial court's finding that the "sudden availability of monoclonals" was the reason for the commercial success of Hybritech's diagnostic kits (Finding 11) is unsupported by the record and clearly erroneous. Monoclonal admits that monoclonal antibodies were available in the United States in 1978, and the evidence clearly reflects that. Thus, at least three years passed between the time monoclonal antibodies were available in adequate supply and the time Hybritech began selling its kits. Especially in the fast-moving biotechnology field, as the evidence shows, that is anything but sudden availability.

ii. Unexpected Advantages

Hybritech points to the testimony of three witnesses skilled in the diagnostic field who state that, based on tests done in their laboratories as a result of real-world comparisons in the normal course of research, the diagnostic kits that embody the '110 invention unexpectedly solved longstanding problems. Dr. Hussa, the head of a large referral laboratory and a world-wide consultant, testified that until Hybritech introduced its kits, he and others were very skeptical and had almost exclusively used competitive assays with a radioactive tracer (RIAs). 5 In relation to an

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HCG Hybritech kit, he testified that he had first thought that the Hybritech HCG kit would not give accurate results for low antigen concentrations because that condition is indicated in the Hybritech kit by a low radioactivity reading, a reading difficult to differentiate from control samples containing no antigen. He also stated that in the past, RIA kits falsely detected HCG in nonpregnant women, a condition which would indicate cancer and surgery. He stated that when he employed the Hybritech HCG kit in such instances it demonstrated, correctly and absent any difficulty interpreting the data, that no HCG was present.

Dr. Blethen, an M.D. holding a Ph.D. in biochemistry, testified that she did not think that the Hybritech HGH kit, for detecting growth hormone in children, would offer any advantage, but she determined that it detected HGH deficiencies in children where conventional RIAs failed to do so. She also stated that the kit does not give false positive readings as do conventional RIA kits, an opinion shared by Dr. Hussa. A third witness, Dr. Herschman, who

holds a master's degree in chemistry, testified that he spent years working on the development of an assay that would determine the presence of TSH (thyroid stimulating hormone) with greater sensitivity. He succeeded but discovered that the Hybritech TSH kit had the same sensitivity; the test being performed in four hours rather than the three days his kit required.

Having considered the evidence of nonobviousness required by Sec. 103 and Graham, supra, we hold, as a matter of law, that the claimed subject matter of the '110 patent would not have been obvious to one of ordinary skill in the art at the time the invention was made and therefore reverse the court's judgment to the contrary. The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumed validity, Lindemann, 730 F.2d at 1462, 221 USPQ at 488, as a whole. See 35 U.S.C. Sec. 103; Jones v. Hardy, 727 F.2d 1524, 1529, 220 USPQ 1021, 1024 (Fed.Cir.1984). Focusing on the obviousness of substitutions and differences instead of on the invention as a whole, as the district court did in frequently describing the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness. See generally Hodosh v. Block Drug Co., 786 F.2d 1136, 229 USPQ 182 (Fed.Cir.1986). 6

With respect to the objective indicia of nonobviousness, while there is evidence that marketing and financing played a role in the success of Hybritech's kits, as they do with any product, it is clear to us on the entire record that the commercial success here was due to the merits of the claimed invention. It cannot be argued on this record that Hybritech's success would have been as great and as prolonged as admittedly it has been if that success were not due to the merits of the invention. The evidence is that these kits compete successfully with numerous others for the trust of persons who have to make fast, accurate, and safe diagnoses. This is not the kind of

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merchandise that can be sold by advertising hyperbole.

V. Enablement, Best Mode, and Definiteness Under Sec. 112

The section 112 defense appears to have been an afterthought of both Monoclonal, who briefly but unsuccessfully attempts to defend this utterly baseless determination, and of the district court which adopted the defense from Monoclonal's pretrial papers apparently without knowledge of the applicable law, to highlight, as it stated at trial, that it was part of its job to see that "whoever wins wins all the way or whoever loses loses all the way." Taken as a whole, the court's comments on Sec. 112--split into two parts, one from Monoclonal's pretrial brief and the other from the adopted pretrial findings and conclusions--are internally inconsistent. The opinion states that the patent fails to disclose how (1) to make monoclonal antibodies; (2) to screen for proper monoclonal antibodies; and (3) to measure monoclonal antibody affinity and therefore the specification is nonenabling and does not satisfy the best mode requirement, and the claims are indefinite. We discuss each of these in turn.

1. Enablement

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, Raytheon Co. v. Roper Corp., 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed.Cir.1983), is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive, Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed.Cir.1984), and is determined as of the filing date of the patent application, which was August 4, 1980. See W.L. Gore and Associates v. Garlock, Inc.,

721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed.Cir.1983). Furthermore, a patent need not teach, and preferably omits, what is well known in the art. Lindemann, 730 F.2d at 1463, 221 USPQ at 489.

The record fully supports the '110 patent's statement that

The monoclonal antibodies used for the present invention are obtained by the [hybridoma] process discussed by Milstein and Kohler.... The details of this process are well known and not repeated here.

The district court itself stated that the "method for producing monoclonal antibodies in vitro was well known prior to the alleged invention of the '110 patent," and used the "sudden availability of monoclonal antibodies" produced by the Kohler and Milstein discovery to support, albeit erroneously, its finding of a lack of nexus between the merits of the claimed invention and its commercial success. The court then about-faced and held the '110 patent deficient because it fails to teach how to make monoclonal antibodies.

With respect to screening, the only permissible view of the evidence is that screening methods used to identify the necessary characteristics, including affinity, of the monoclonal antibodies used in the invention were known in the art and that the '110 patent contemplated one of those. At trial, Monoclonal's counsel stated "it is a procedure that was known in '78." In similar fashion, the district court held that the claimed subject matter would have been obvious in part because the "existence of monoclonal antibodies having the affinity constants claimed in the patent was well known prior to the alleged invention...." [Emphasis ours.] Furthermore, there was not a shred of evidence that undue experimentation was required by those skilled in the art to practice the invention. We hold as a matter of law that the '110 patent disclosure is enabling.

2. Best Mode

"The specification ... shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. Sec. 112. Because not complying with the best mode requirement amounts to concealing the preferred mode contemplated by the applicant at the time of filing, in order to find that the best mode requirement is not satisfied, it must be shown that

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the applicant knew of and concealed a better mode than he disclosed. DeGeorge v. Bernier, 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed.Cir.1985) (quoting with approval In re Sherwood, 613 F.2d 809, 204 USPQ 537 (CCPA 1980)). The only evidence even colorably relating to concealment is testimony by various Hybritech employees that sophisticated, competent people perform the screening and that the screening process is labor-intensive and time-consuming. It is not plausible that this evidence amounts to proof of concealment of a best mode for screening or producing monoclonal antibodies for use in the claimed '110 process, and therefore we are of the firm conviction that the district court's finding that the best mode requirement was not satisfied is clearly erroneous.

3. Indefiniteness

The basis of the district court's holding that the claims are indefinite is that "they do not disclose how infringement may be avoided because antibody affinity cannot be estimated with any consistency." (Conclusion 6.) Even if the district court's finding in support of this holding--that "there is no standard set of experimental conditions which are used to estimate affinities"--is accurate, under the law pertaining to indefiniteness--"if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more," Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624,

225 USPQ 634, 641 (Fed.Cir.1985)--the claims clearly are definite. The evidence of record indisputably shows that calculating affinity was known in the art at the time of filing, and notwithstanding the fact that those calculations are not precise, or "standard," the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more.

VI. Motions

Monoclonal's motion to strike Appendices A and B of Hybritech's reply brief as being beyond the page limit applicable to reply briefs is granted as to Appendix A but denied as to Appendix B, the latter having been helpful in culling the often non-supportive citations to the record by Monoclonal.

Hybritech's motion to supplement the record with a Monoclonal advertisement not considered at trial is denied. Any adverse impact that the disposition of these two motions has upon either party is more than outweighed by this court's patience with the seemingly endless flow of post-argument argumentative papers.

VII. Conclusion

The judgment of the district court holding the patent in suit invalid is reversed in all respects, and the case is remanded for a determination of the issue of infringement which the court held was moot.

REVERSED AND REMANDED.

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1 With respect to obviousness, one portion of the district court's opinion apparently relies on all of the above listed references, (1)--(5), for the obviousness holding while a later portion entitled "CONCLUSIONS OF LAW" relies on only the Oi/Herzenberg and Frankel articles. Furthermore, the district court did not state that the LJCRF work was considered for purposes of Sec. 103, although we recognize that Sec. 103(g) prior art can be used for Sec. 103.

2 A dose response curve is antigen concentration plotted against the signal produced by labelled antibody in an immunoassay. The signal increases with increasing antigen concentration in a successful assay but at some point decreases when the antigen concentration becomes too high.

3 Although the district court failed expressly to find the level of ordinary skill in the art at the time the invention was made, it did make reference to "[p]eople working in immunology aware of the Kohler and Milstein discovery" which we deem an accurate finding for the purposes of that portion of the Graham factual inquiries.

4 Finding 10, which states that the invention was contemporaneously developed and disclosed in at least five publications and patent applications not listed above and dated well after the filing date of the '110 patent but before its issuance is irrelevant for purposes of the hypothesis based on the three factual inquiries required by Sec. 103 as interpreted by Graham v. John Deere, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 USPQ 459 (1966) because obviousness must be determined as of the time the invention was made. Additionally, they are of little probative value in this case because they are dated December 1981 at the earliest, more than a year after the August 4, 1980, filing date here and roughly two years after conception occurred. Furthermore, simultaneous development may or may not be indicative of obviousness, the latter being the case here for the above reasons and because the other evidence of nonobviousness is adequate, such occurrences having been provided for in 35 U.S.C. Sec. 135. Lindemann, supra, 730 F.2d at 1460-61, 221 USPQ at 487; Environmental Designs, Ltd. v. Union Oil Co. of California, 713 F.2d 693, 698 n. 7, 218 USPQ 865, 869 n. 7 (Fed.Cir.1983).

5 Monoclonal's expert Blakemore testified that of 425 assays on the market in 1979 less than 1% were sandwich assays. Today, sandwich assays constitute the majority of all assays sold.

The record also shows that Blakemore, who testified extensively for Monoclonal that the claimed invention would have been obvious, never used monoclonal antibodies in sandwich assays at Bio-Rad before 1980. Additionally, she did not even mention them in the Jeong patent, of which she was a coinventor, which issued January 13, 1981, long after the beginning of Hybritech's work in this area in 1979.

6 It bears repeating that it is crucial that counsel set forth the law accurately. More particularly, it is the duty of counsel to impart to the judge that the obviousness question properly is whether the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made, and that the district court must expressly make the three factual determinations required by Graham and consider objective evidence of obviousness before the legal conclusion of obviousness vel non is made. Submitting to the court language like "any differences ... would have been obvious," as was done here, violates the axiom that the question is not whether the differences would have been obvious but the claimed invention as a whole. Furthermore, arguing that "it would be obvious" rather than that it would have been obvious shifts the court's focus to the wrong period of time, namely to a time long after the invention was made, in which, more likely than not, the prior art and the level of ordinary skill in the art are more advanced. See 35 U.S.C. Sec. 103.